ACTA SCIENTIFIC NUTRITIONAL HEALTH

Volume 3 Issue 2 February 2019

Review Article

The Scourge of Our Time, Alzheimer's Disease, can be Prevented by Two Simple Steps

Brewer GJ*

Departments of Human Genetics and Internal Medicine, University of Michigan, USA

***Corresponding Author:** Brewer GJ, Departments of Human Genetics and Internal Medicine, University of Michigan, USA.

Received: December 27, 2018; **Published:** January 08, 2019

Abstract

Background: The current prevalence of Alzheimer's disease (AD) in developed countries is so high that it is clear an epidemic of AD is occurring. There are two important facts about this epidemic that point to the likely cause. The first is it is occurring in developed countries only. The second is the epidemic is relatively new, developing after 1900. These two facts point to the likely cause being an environmental change occurring in developed countries after 1900. After carefully reviewing the evidence for and against possible causative environmental agents or factors in a previous publication, we identified ingestion of divalent copper specifically, and total copper generally, as the causative agents.

Methods and Results: The evidence incriminating ingestion of divalent copper, first involves AD animal studies, in which tiny amounts of divalent copper added to the animals' drinking water greatly enhanced AD. The EPA allows ten times more copper in US human drinking water than used in the animals. US human drinking water samples with high copper levels, are very common. Copper plumbing use increased dramatically in the 1900s. The curves of AD prevalence and copper plumbing use match each other closely. In human's ingestion of divalent copper containing supplement pills is associated with cognition loss at six times the rate in other groups. Food copper is mostly monovalent copper. Thus, humans evolved ingesting primarily monovalent copper, and developed safe ways of handling and channeling monovalent, but not divalent copper.

A mild increase in body copper load is also a risk factor for AD. Copper is much better absorbed from meat than from vegetable foods. There is good evidence that meat eating increased sharply in the 1900's in developed countries, thus probably increasing body copper load.

Conclusion: It is clear that increased ingestion of divalent copper is a major causative factor in the AD epidemic. Thus, up to 95% of AD cases in developed countries can be prevented by not using copper supplement pills, and by testing drinking water for copper levels. If the latter is over 0.01 parts per million, a copper removal device should be placed on the drinking/cooking water tap. Cutting down on meat eating will also likely help in preventing AD.

Keywords: Alzheimer's Disease; Divalent Copper; Prevention of Alzheimer's Disease; Drinking Water Copper; Supplement Pill Copper

Abbreviations

AD: Alzheimer's Disease; Aβ: Amyloid Beta; US: United States.

Introduction

There is little question that Alzheimer's disease (AD), is a major scourge of our time. By robbing us of our memories, and our thinking ability, it removes what makes us human. We remain alive, but become more and more like pet animals, requiring 24/7 care. There are many other bad diseases, and while they may maim and may be painful, they don't rob us of our cognition and what makes us human, at least not in the huge numbers that AD does.

Speaking of the numbers that AD is afflicting, about 15% of us that reach age 67 to 74, and 44% of those age 75 to 84 develop AD [1]. These numbers mean the prevalence of AD has reached epidemic proportions. And there are two very interesting and

important epidemiologic and historical facts about this epidemic that most people don't realize. First, the epidemiologic fact: The epidemic of AD only involves developed countries. Undeveloped countries have a low prevalence of AD amongst their elderly. For example, in India, AD prevalence is 1.07% in those 65 and older [2]. In Nigeria, Africa, the prevalence of AD in those aged 65 to 74 is 0.52%, and in those aged 75 to 84, it is 1.69% [3]. Now the historical fact: The epidemic is new, in the sense that it has occurred since 1900. The evidence is strong that before 1900, the prevalence of AD was quite low in developed countries. As evidence of this, important medical scientists involved with the brain and publishing in the late 1800s and early 1900s did not discuss a disease like AD. For example, Gowers [4] wrote a textbook of Neurology and discussed no such disease. Osler [5] wrote a series of books gathering all medical information together, including an entire volume on the brain, and there was no mention of a disease like AD. Freud [6] published extensively on brain abnormalities manifested as various types of psychological symptoms and did not mention a disease like AD. Boyd [7] wrote a textbook of pathology, and there was no mention of amyloid plaques and neurofibrillary tangles, hallmarks of AD pathology, in the brains at autopsy.

Faced with these facts, some have argued that since AD is a disease of aging, there were simply not enough elderly people in the period around 1900 to manifest the disease. But this argument is invalidated simply by looking at census data. In 1900 the US census shows there were over 3 million people aged 60 and over, plenty of people to manifest the disease if it were present at today's rate. In France in 1911 [8] there were 255,000 people aged 65 to 75, and 115,000 people aged 75 to 85, again providing many patients if the disease had a high prevalence like now.

A second argument is that since the disease AD wasn't recognized and named until 1907 [9], people didn't recognize AD as a separate disease, but simply attributed AD patients as manifesting normal aging of the brain. While this conceivably could account for clinicians, such as Gower, Osler, and Freud, missing the disease, although it seems unlikely because of their comprehensive work and thoroughness, it would not account for pathologists such as Boyd not seeing amyloid plaques and neurofibrillary tangles in brains at autopsy.

Given the above, it seems clear the two historical and epidemiological facts are valid. These facts are important, because the most likely explanation for them is that an environmental agent or agents, introduced after 1900 in developed but not undeveloped countries, is causing the AD epidemic. And this conclusion is important because if this agent or agents can be identified, it should be possible to eliminate the agent or agents and quell the epidemic of this terrible scourge.

A number of agents, and even life style changes, have been put forward as an environmental cause of AD. The author has written a book on this topic [10]. One chapter was dedicated to examining the evidence for these various putative causes of the AD epidemic. To be considered a likely cause of the AD epidemic, an agent or other proposed cause had to pass two tests. One test was that exposure to the agent, or other proposed cause, had to fit the epidemiological and historical facts of the epidemic. That is the exposure had to dramatically change after the 1900s in developed countries but not in undeveloped countries. Second, the proposed agent or other cause had to have a rational pathophysiological mechanism by which it could cause AD.

After weighing all the evidence, two agents passed these tests [10]. One was increased ingestion of divalent copper (which for convenience will be referred to as copper 2 from here on).

The second was increased ingestion of total copper. These two topics will now be taken up separately.

Copper 2 ingestion as a cause of the AD epidemic

In 2003, Sparks and Schreurs [11], published a paper showing that tiny amounts (0.12 parts per million or ppm) of copper added to the drinking water of a rabbit model of AD greatly enhanced the amyloid plaques in the brain, and damaged the animals' memories. The Environmental Protection Agency (EPA) allows 1.3 ppm copper in human drinking water in the US [12], ten times the amount shown toxic in the animal model studies. The finding that tiny amounts of copper greatly enhances AD in animal models has been shown in several AD animal models besides the rabbit [13] and has also been confirmed in another laboratory [14]. Then, in 2006, Morris., *et al*. [15] published a paper on the intake of various nutrients and their relationship to cognition loss over a period of several years in a large Chicago population. They found that those in the highest quintile of copper intake, and they were there because of ingestion of a copper-containing supplement pill, if they also at a high fat diet as many do these days in developed countries, lost cognition at six times the rate of other groups!

What do the AD animal model studies [11] and the Morris., *et al*. [15] studies have in common? Yes, they both involve copper, but beyond that, they involve a special form of copper, that is they both involve ingesting copper 2. And why is ingesting copper 2 of great note? Because a 2014 study of copper speciation in food indicates that copper in food is almost all monovalent copper (copper 1) [16]. This is a bit surprising because copper 1 and copper 2 in living tissue work as a redox doublet, catalyzing many important reactions important in life. But apparently, at death or harvest, in the absence of oxygen transport, most of the copper 2 is reduced to copper 1. Knowing that copper in food is primarily copper 1 is very important, because it means that our ancestors evolved ingesting primarily copper 1 and weren't exposed to copper 2.

Free copper is a very toxic element and has to be kept carefully bound. The fact that during evolution we were exposed to copper 1 (but not copper 2) explains why we have evolved a very careful system for safely channeling copper1, but not copper2. For example, the intestinal cell has a copper receptor, Ctr1 [17], but Ctr1 will only accept copper 1 and not copper 2. As a result, after absorption, copper 1 is channeled to the liver, where it is attached to appropriate proteins. In contrast, a significant proportion of ingested copper 2 is absorbed directly into the blood, and some ends up in the brain and is toxic to cognition over a period of time. This difference in absorption patterns can be seen in radiolabeling studies. If food copper (which is copper 1) is radiolabeled before ingestion, none of the label will appear in the blood until 1-2 days, and the labeled copper in the blood will all be safely bound to proteins secreted by the liver. In contrast, when radiolabeled copper is ingested as a simple salt (meaning it is copper2) upwards of 50% of the administered dose appears in the blood in 1-2 hours [18], much too fast to be processed by the liver.

So, we know copper 2 is not channeled safely, but next, does it pass the two tests of causing the AD epidemic? The first test is appropriate exposure in developed countries but not undeveloped countries after 1900. What immediately comes to mind is the use of copper plumbing, but does copper plumbing leach enough copper 2 into human drinking water to cause AD? The answer to this question is yes, using the AD animal model studies as a guide to how much copper in drinking water is required to cause AD. A study [19] of copper content in 280 drinking water samples from all over N. America revealed that about 1/3 of the samples had copper content at or above the 0.1 ppm level found toxic in animal models, about 1/3 were below 0.01 ppm and are deemed as safe, and 1/3 are between 0.1 and 0.01 ppm and are of unknown safety because those levels haven't been studied. The likelihood of copper 2 causing the AD epidemic is increased by comparing the epidemic of AD temporally to the "epidemic" of use of copper plumbing in developed countries. The AD prevalence gradually increased in the early 1900s, and then after 1950, increased explosively to today's prevalence. The use of copper plumbing started in the early 1900s, was curtailed by two world wars, and then exploded after 1950 so that now over 90% of US homes have copper plumbing [20]. The two prevalences, AD and the use of copper plumbing, are remarkably similar over time.

An interesting and very supportive fact about copper plumbing being an important factor in AD causation can be found in considering the Japanese. Japan is a developed nation with a low prevalence of AD [21], and they have shunned the use of copper plumbing for fear of toxicity. Yet, when Japanese migrate to Hawaii, where copper plumbing is used, their prevalence of AD increases to that of other developed countries [22].

In addition to drinking water leaching copper 2 from copper plumbing as a source of copper 2, ingestion in the 1900s, it became common for people in developed countries to take a multi-mineral supplement pill containing copper. This copper is also all copper 2, and we know from the Morris., *et al.* [15] studies that this type of ingested copper is associated with rapid cognition loss.

From the above evidence we can conclude that copper 2 as a causative agent of the AD epidemic fulfills the first test we listed, that is, due to copper 2 in drinking water and from copper 2 containing supplement pills, exposure to ingestion of considerable copper 2 occurred in the 1900s, but only in developed countries, not undeveloped countries. But what about the second test, is there a rational pathophysiological mechanism for copper 2 to cause AD? The answer is, yes there is.

The plaques in the brains of AD patients are composed of aggregated Aβ, which is a small protein cleaved from the larger amyloid precursor protein. Aβ, as such is a soluble protein that is present at low levels in the normal brain. In the AD brain it accumulates at higher levels and aggregates into amyloid plaques. These amyloid plaques are neurotoxic [23], and are thought to be critically involved in the pathogeneses of AD. What causes the Aβ to aggregate in the AD brain? It turns out copper 2 causes "dramatic aggregation of Aβ, particularly under conditions of "physiological acidosis" [24]. This mild acidosis can be caused by inflammation, for example as induced by oxidative damage. The neurotoxicity of

amyloid plaques is one of producing oxidative damage due to release of H_2O_2, which results from copper 2 binding to the plaques [23]. Thus, a vicious cycle, copper 2 causes Aβ aggregation, which causes oxidative damage, inflammation, and more acidosis, which produces more copper 2 Aβ aggregation.

A second mechanism of copper 2 causation of neurotoxicity in AD has recently been proposed [25]. It was noted that the insoluble Aβ plaques in the brains of AD patients contained high concentrations of advanced glycation end-products (AGEs). It was shown that glycation of Aβ with sugars generates significant amounts of superoxide anion, which in the presence of copper 2, is converted to hydroxyl radical, which causes oxidative damage, including DNA damage [25]. It was shown that all three components in AD plaques, Aβ, sugar, and copper 2 are necessary to produce oxidative damage [25]. Thus, it is clear that there are pathophysiological mechanisms of oxidative damage and brain inflammation, hallmarks of the AD brain, intimately involving a critical role for copper 2.

Increased body copper load, irrespective of copper valence, as a second cause of the AD epidemic

Total body copper loading as a factor in AD derives primarily from the studies of the Squitti group in Italy, First, they have shown the blood free copper level is elevated in AD [26]. The copper in blood can be thought of as in two pools. 85-90% of blood copper is safely and covalently bound in ceruloplasmin (Cp). The second smaller pool is copper loosely bound to albumin and other molecules and is the freely available copper to fill the body's daily needs for copper. This smaller pool is called "free copper", but it is not really free, just more loosely bound. If the free copper pool becomes increased, as it is greatly increased in untreated Wilson's disease, the copper becomes toxic. Thus, it is very significant to find this pool increased in AD [26], although it is not nearly increased as much as it is in untreated Wilson's disease.

The Squitti group has done additional work that ties the free copper levels in AD to the pathogenesis of the disease. They have shown that the free copper levels correlate with cognition scores in AD, that is the higher the free copper levels, the lower the cognition scores [27].

Then, they have shown that the level of free copper predicts the rate of cognition loss over time, that is, the higher the level of free copper, the greater the rate of cognition loss [28]. Lastly, they have shown that the higher the blood free copper level, the greater the risk of mild cognitively impaired (MCI) patients, the precursor state to AD, to convert to full blown AD [29]. All these pieces of data of the Squitti group tie the free copper levels very closely to AD pathogenesis, and indicates that, at least in some patients, AD is a disease of copper toxicity. Of course, this work ignores copper valence, so it just indicates that copper toxicity, irrespective of valence, is playing a role in AD.

The Squitti group have done additional work which sheds light on the situation. They have found that there is an increased prevalence of ATP7β mutant genes in the AD patient population [30]. This means that possessing an ATP7B mutant gene increases the risk of having AD. The ATP7β gene is the Wilson's disease gene. Wilson's disease, a disease of severe copper toxicity, is recessive, meaning that both copies of ATP7β have to be disabled to cause the disease. But studies of Wilson's disease families have revealed that heterozygous carriers of one copy of a disabled ATP7β gene have a mild increase in body copper loading, as manifested by a mild increase in liver and urine copper. Assuming the patients with an ATP7B mutant allele the Squitti., *et al.* [30] group find at increased prevalence in the AD population also have an increased body copper load, this means a mild increased body copper load is a risk factor for AD. This then raises the question, is there any way a mild increase in body copper load could be a factor in causing the AD epidemic? Of course, it couldn't be a change in the prevalence of ATP7B mutant genes, because these prevalences don't change as quickly as would be necessary to be a factor in the AD epidemic. But, is there some other mechanism whereby a mild increase in body copper loading could play a role in the sudden explosion of the AD epidemic in the 1900's?

The answer is yes, and it lies in dietary changes resulting in increased meat eating in the 1900s in developed countries.

It is estimated that there is about 50% more copper absorbed from meat than from an equal amount of vegetable foods [31]. This is because copper in meat is much more bioavailable than from vegetable foods, due to the high content of phytate, fiber, and other copper binding substances, in vegetable foods. As a result of greater use of meat animal food lots in developed countries, and increasing poultry consumption, it is estimated in the 1900s that meat consumption increased by 35% in the US [32,33]. Thus, the increased meat eating in the 1900s, resulting in a mild body copper load, has probably also contributed to the AD epidemic.

Preventive Measures to Take to Cause Abatement of the AD Epidemic

If we can abate the AD epidemic it should eliminate about 95% of the cases of AD. That number comes from assuming that the current prevalence of AD in developed countries is about 20%, and that the baseline prevalence, in the absence of the epidemic, is about 1%, as it is currently in undeveloped countries. Thus abating 19% out of 20%, or 19/20, is abating 95% of the cases. This would be a major accomplishment and save a huge amount of misery in terms of having to live a partially meaningless life, caregiving time, and money, so it is very important to do it if possible. If the proposal here is correct, it should be straightforward to accomplish this mission by carrying out the two preventive measures listed below. What is the likelihood the two causative mechanisms proposed here, copper 2 ingestion and increased body copper loading from increased meat eating, are correct? The likelihood seems very high, given the totality of the evidence. Given this situation, it seems very wise to seize on the preventive measures presented below, because of the very favorable odds that it will result in preventing this scourge of a disease, and the preventive measures are not that difficult or onerous.

The first preventive measure is to throw away, or not buy in the first place, any multi-mineral supplement pill, because they all contain copper 2. There is a company (Mito Synergy) that now makes copper 1 supplement pills for those who must take copper supplements because of certain diseases.

The second measure is to check the copper content of the household drinking water. There are many companies that offer this service. This should be done even if copper plumbing is not in use, because in some areas the source water is high in copper. if the level is 0.01 ppm or lower, it is safe. If it is higher than that, the copper plumbing doesn't have to be removed. Simply add a copper removal device, such as a reverse osmosis device, to the tap used for drinking and cooking water.

These two measures will take care of excess copper 2 ingestion. As for increased body copper loading due to meet eating, it is not certain how much to reduce meat eating to obtain the desired result, but a 50% reduction could be a reasonable estimate. This level of meat reduction could be a very healthy move anyway, because according to Sinha., *et al*. [34], a 50% reduction in meat eating would reduce overall mortality by 42%. Of course, of all the preventive measures, a reduction in meat eating is by far the hardest since it involves a change in lifestyle. It may be less important than the copper 2 preventive measures, based on the Japanese experience. In that case, moving from Japan, and low copper 2 ingestion due to lack of copper plumbing, to Hawaii with a higher copper ingestion, made all the difference. It seems unlikely that the diet changed enough to affect meat ingestion and body copper loading.

Conclusion

In conclusion, we have first discussed that developed countries have an epidemic of AD with a very high prevalence of the disease, while undeveloped countries have a low prevalence of around 1%. Second, we have shown that the AD epidemic in developed countries is relatively new, developing in the 1900s. We have emphasized how important these two facts are in trying to determine the cause of the epidemic, namely they point to an environmental factor or factors with exposure in developed countries only occurring in the 1900s. In a previous publication [10], we have exhaustively reviewed data and information about possible environmental agents that could cause the epidemic and determined that two possibilities stand out. One is exposure to divalent copper, here called copper2. It was pointed out that food copper is primarily monovalent copper, and thus evolution caused development of ways to handle potentially toxic copper, but only for monovalent but not divalent copper. Humans began to be exposed to much divalent copper for the first time with the advent of copper plumbing, but in developed countries only. Copper plumbing began to be used in the early 1900s and increased rapidly after 1950, so that now 90% of US homes have copper plumbing. It has been shown that enough copper is leached from copper plumbing to cause AD, according to AD animal model studies, which show that tiny amounts of divalent copper in drinking water causes severe AD. The increasing prevalence of use of copper plumbing in the 1900s closely parallels, timewise, the increasing prevalence of AD. It has also been shown that ingestion by humans of copper supplement pills in which the copper is always divalent copper, is associated with rapid loss of cognition, leading to the conclusion that the common practice of ingesting multimineral supplement pills, which always contain copper, is another factor in the AD epidemic.

The second agent possibly contributing to the epidemic is increased ingestion of total copper, irrespective of valence, due to increased meat eating in the 1900s in developed countries. Copper is much better absorbed from meat than from vegetable foods, and this may cause a mild increase in total body copper loading. There is evidence that a mild increase in body copper loading is a risk factor for AD.

If the agents proposed here as causing the epidemic are correct, 95% of AD cases, those that are part of the AD epidemic, can be prevented by avoiding ingestion of divalent copper, and reducing meat eating. Divalent copper should now be viewed as a toxic element.

Bibliography

1. Alzheimer's Disease Association "Facts and Figures". Alzheimer's Association National Office: Chicago, IL. (2016).

2. Chandra V., *et al*. "Prevalence of Alzheimer's disease and other dementias in rural India". *Neurology* 51 (1998): 1000-1008.

3. Hendrie., *et al*. "Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans". *The American Journal of Psychiatry* 152 (1995): 1485-1492.

4. Gowers WR. "A Manual of Diseases of the Nervous System". P Blakiston, Son, and Co., Philadelphia, PA. (1888).

5. Osler W. "Modern Medicine: Its Theory and Practice". Lea and Febiger, Philadelphia, PA (1910).

6. Strachey J., *et al*. "The Standard Edition of the Complete Psychological Works of Sigmund Freud, Written between 1895 and 1939". The Hogarth Press and the Institute of Psychoanalysis, London. (1966).

7. Boyd WA. "Textbook of Pathology: An Introduction to Medicine". Lea and Febiger, Philadelphia (1938).

8. Waldman M and Lamb M. "Dying for a Hamburger: Modern Meat Processing and the Epidemic of Alzheimer's Disease". Thomas Dune Books/St. Martin's Press, New York, (2005).

9. Alzheimer A. "Uber eine eigenartige Erkankung der Hirnrinde". *Allg Z Psychiatric* 64 (1907): 146-148.

10. Brewer GJ. "Environmental Causes for Alzheimer's Disease and Prevention Measures". *Academic Press* (2018).

11. Sparks DL and Schreurs BG. "Trace amounts of copper in water induce beta-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease". *Proceedings of the National Academy of Sciences of the United States of America* 100 (2003): 11065-11069.

12. National Research Council. "Copper in Drinking Water". National Academy Press, Washington DC. (2000).

13. Sparks DL., *et al*. "Trace copper levels in the drinking water, but not zinc or aluminum, influence CNS Alzheimer-like pathology". *The Journal of Nutrition Health and Aging* 10 (2006): 247-254.

14. Singh I., *et al*. "Low levels of copper disrupt brain amyloid-beta homeostasis by altering its production and clearance". *Proceedings of the National Academy of Sciences of the United States of America* 110 (2013): 14771-14776.

15. Morris MC., *et al*. "Dietary copper and high saturated and trans-fat intakes associated with cognitive decline". *Archives of Neurology* 63 (2006): 1085-1088.

16. Ceko MJ., *et al*. "Speciation of copper in a range of food types by x-ray absorption spectroscopy". *Food Chemistry* 164 (2014): 50-54.

17. Ohrvik H and Thiele DJ. "How copper transverses cellular membranes through the copper transporter I, Ctrl". *Annals of the New York Academy of Sciences* 1314 (2014): 32-41.

18. Hill GM., *et al*. "Treatment of Wilson's disease with zinc. II Validation of oral 64 copper with balance". *The American Journal of the Medical Sciences* 292 (1986): 344-349.

19. Brewer GJ. "Copper excess, zinc deficiency, and cognition loss in Alzheimer's disease". *Biofactors* 38 (2012): 107-113.

20. Foley PT. "International Copper Demand Patterns: The Case of Plumbing Tube". Economics of Internationally Traded Minerals, Economics of Copper, CRU Consultants Inc. NY Section 5.2 (1985): 183-186.

21. Ueda K., *et al*. "Prevalence and etiology of dementia in a Japanese community". *Stroke* 23 (1992): 798-803.

22. White L., *et al*. "Prevalence of dementia in older Japanese-American men in Hawaii: The Honolulu-Asia Aging Study". *JAMA* 276 (1996): 955-960.

23. Huang X., *et al*. "Cu(II) Potentiation of Alzheimer Aβ Neurotoxicity". *Journal of Biological Chemistry* 274.52 (1999): 37111-37116.

24. Atwood CS., *et al*. "Dramatic Aggregation of Alzheimer AB by Cu(II) Is Induced by Conditions Representing Physiological Acidosis". *Journal of Biological Chemistry* 273.21 (1998): 12817-12826.

25. Fica-Contreras SM., *et al*. "Clycation of Lys-16 and Arg-5 in amyloid-B and the presence of CU2+ play a major role in the oxidative stress mechanism of Alzheimer's disease". *Journal of Biological Inorganic Chemistry* 22 (2017): 1211-1222.

26. Squitti R., *et al*. "Excess of serum copper not related to ceruloplasmin in Alzheimer disease". *Neurology* 64 (2005): 1040-1046.

27. Squitti R., *et al*. "Excess of nonceruloplasmin serum copper in AD correlates with MMSE, CSF [beta]-amyloid, and h-tau". *Neurology* 67 (2006): 76-82.

28. Squitti R., *et al*. "Longitudinal prognostic value of serum "free" copper in patients with Alzheimer's disease". *Neurology* 72 (2009): 50-55.

29. Squitti R., *et al*. "Value of serum nonceruloplasmin copper for prediction of mild cognitive impairment conversion to Alzheimer disease". *Annuals of Neurology* 75 (2014): 574-580.

30. Squitti R., *et al*. "ATP7B variants as modulators of copper dyshomeostatis in Alzheimer's disease". *Neuro Molecular Medicine*15 (1993): 515-522.

31. Brewer GJ., *et al*. "Does a vegetarian diet control Wilson's disease?". *Journal of the American College of Nutrition* 12 (1993): 527-530.

32. Cordain L., *et al*. "Origins and evolution of the Western diet: health implications for the 21st century". *The American Journal of Clinical Nutrition* 81 (2005): 341-354.

33. Teicholz N. "How Americans Got Red Meat Wrong". *The Atlantic* 2 (2014).

34. Sinha., *et al*., "Meat Intake and Mortality, A Prospective Study of Over Half a Million People". *JAMA Internal Medicine* 169 (2009): 562-571.

Volume 3 Issue 2 February 2019

© All rights are reserved by Brewer GJ.